



[Billing Code: 4140-01-P]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Center for Advancing Translational Sciences (NCATS): Cooperative Research and Development Agreement (CRADA) and Licensing Opportunity for small molecule inhibitors of the human USP1/UAF1 complex(1) for the treatment of cancer

SUMMARY: The National center for Advancing Translational Sciences (NCATS) and its collaborator, the University of Delaware, are seeking Cooperative Research and Development Agreement (CRADA) partners to collaborate in the final stages of lead optimization, evaluation and preclinical development of a novel series of selective and potent small-molecule inhibitors of the human USP1/UAF1 complex(1) for the treatment of cancer. Interested potential CRADA partners will receive detailed information about the project after signing a confidential disclosure agreement (CDA) with NCATS and University of Delaware.

DATES: Interested candidate partners must submit a statement of interest and capability to the NCATS point of contact before **[INSERT DUE DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER]** for consideration. Guidelines for the preparation of a full CRADA proposal will be communicated shortly thereafter to all respondents with whom initial confidential discussions will have established sufficient mutual interest. CRADA applications submitted after the due date may be considered if a suitable CRADA collaborator has not been

identified by NIH and its collaborator, the University of Delaware, among the initial pool of respondents. Licensing of background technology related to this CRADA opportunity is also available to potential collaborators.

ADDRESSES: Questions about licensing opportunities of related background technology should be addressed to Jenny Wong, M.S., Senior Licensing and Patenting Manager, Office of Technology Transfer, NIH, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852-3804, Telephone: (301) 435-4633; E-mail: wongje@mail.nih.gov. Respondents interested in licensing will be required to submit an “Application for License to Public Health Service Inventions.” An executed CDA will be required to receive copies of the patent applications.

FOR FURTHER INFORMATION CONTACT: Further details of this CRADA opportunity and statement of interest please contact Lili Portilla, M.P.A., Director of Strategic Alliances , National Center for Advancing Translational Sciences, NIH, 9800 Medical Center Drive, Room 311, Rockville, MD, 20850; Telephone (301)-217-2589; E-mail: Lilip@nih.gov or Dr. Krishna Balakrishnan, Senior Technology Transfer Manager, NCATS, Telephone: (301) 217-2336; Email: balakrik@mail.nih.gov

SUPPLEMENTARY INFORMATION: Ubiquitin-specific proteases (USPs) have in recent years emerged as a promising therapeutic target class in the ubiquitin-proteasome system (UPS). Velcade® (bortezomib), a small molecule proteasome inhibitor, has established the ubiquitin-proteasome system as a valid target for anticancer treatment. However, proteasome inhibitors in general suffer from a narrow therapeutic index and acquired resistance. A promising alternative to proteasome inhibition has been to target the enzymes upstream of proteasome-mediated protein

degradation, i.e. the ubiquitin ligases and deubiquitinating enzymes (DUBs), to generate more specific, less toxic therapeutic agents.

The advantage of inhibiting DUB lies in the specificity of therapeutic intervention that can lead to better efficacy and reduced side effects. It has become clear that the DUB activities are indispensable for the normal cellular functions. Abnormal cellular expression of DUBs or the loss of function due to mutation in certain DUB genes have been linked to various human diseases(2, 3). Among the five DUB subfamilies, ubiquitin-specific protease (USP) is emerging as promising targets for pharmacological intervention because of their connection to many human diseases, including prostate, colon and breast cancer, pediatric acute lymphoblastic leukemia, and familial cylindromatosis(2, 4). From the past successes in targeting proteases with small molecule antagonists, it is expected that efforts of targeting human USPs will lead to potent and specific therapeutic agents.

The human ubiquitin-specific protease 1 (or USP1) occupies a special position because it has been implicated in DNA damage response in higher vertebrates and humans. Previous studies showed that disruption of USP1 in chicken DT40 cells resulted in increased sensitivity to DNA crosslinkers(5) and knockout of the murine USP1 gene in a mouse model resulted in hypersensitivity to mitomycin C(6). Previously we have demonstrated that inhibiting the cellular activity of human USP1 by pharmacologically active small molecules sensitized cisplatin-resistant non-small cell lung cancer (NSCLC) cells to DNA crosslinking agent(77). Thus, USP1 inhibitors hold promise in combination therapy with the existing anti-cancer drugs to improve the efficacy and lower the toxic effect of the existing drugs.

More recently we have developed small molecules that target the USP1/UAF1 DUB complex(1). These compounds were identified via a high-throughput screen and subjected to medicinal chemistry optimization, leading to one of the most potent and selective DUB inhibitors

reported to date. Moreover, the inhibitors act synergistically with cisplatin, a DNA damaging anti-cancer drug, to overcome chemoresistance and enhance cytotoxicity. These results suggest the inhibitors may also improve the efficacy and potency of other commonly prescribed chemotherapeutic agents that are known to induce DNA damage. Furthermore the USP1/UAF1 small molecule inhibitors also hold promise in the single-agent therapy.

Under the CRADA, the chemical series will be further characterized and optimized to address specific aspects of this target product profile. The CRADA scope will also include studies beyond candidate selection including all aspects of preclinical studies such as toxicity studies, xenograft studies and chemistry GMP scale up of selected compounds and manufacture of control leading to a successful investigational new drug (IND) application. Collaborators should have experience in pre-clinical development of small molecules with a focus on cancer and a track record of successful submission of IND applications to the FDA.

The full CRADA proposal should include a capability statement with a detailed description of (1) collaborator's expertise in the areas of modulation of small molecule physicochemical and pharmacokinetic properties; (2) expertise in formulation of small molecules and ability to manufacture sufficient quantities of chemical compounds according to FDA guidelines and under Good Manufacturing Practice (GMP); (3) expertise with oncology and/or other diseases which may benefit from USP1/UAF1 inhibition; (4) expertise in regulatory affairs, particularly at the IND filing and early clinical trial stages; (5) collaborator's ability to support, directly or through contract mechanisms, and ability, upon the successful completion of relevant milestones, to support the ongoing pharmacokinetics and biological studies, long term toxicity studies, process chemistry and other pre-clinical development studies needed to obtain regulatory approval of a given molecule so as to ensure a high probability of eventual successful commercialization; (6) collaborator's ability to provide adequate funding to support some of the project's pre-clinical studies.

Publications:

1. Liang, Q., Dexheimer, T. S., Zhang, P., Rosenthal, A. S., Villamil, M. A., You, C., Zhang, Q., Chen, J., Ott, C. A., Sun, H., Luci, D. K., Yuan, B., Simeonov, A., Jadhav, A., Xiao, H., Wang, Y., Maloney, D. J., and Zhuang, Z. (2014) A selective USP1-UAF1 inhibitor links deubiquitination to DNA damage responses, Nature chemical biology **10**, 298-304.
2. Singhal, S., Taylor, M. C., and Baker, R. T. (2008) Deubiquitylating enzymes and disease, BMC Biochem **9 Suppl 1**, S3.
3. Reyes-Turcu, F. E., Ventii, K. H., and Wilkinson, K. D. (2009) Regulation and cellular roles of ubiquitin-specific deubiquitinating enzymes, Annu Rev Biochem **78**, 363-397.
4. Hussain, S., Zhang, Y., and Galardy, P. J. (2009) DUBs and cancer: the role of deubiquitinating enzymes as oncogenes, non-oncogenes and tumor suppressors, Cell Cycle **8**, 1688-1697.
5. Oestergaard, V. H., Langevin, F., Kuiken, H. J., Pace, P., Niedzwiedz, W., Simpson, L. J., Ohzeki, M., Takata, M., Sale, J. E., and Patel, K. J. (2007) Deubiquitination of FANCD2 is required for DNA crosslink repair, Mol Cell **28**, 798-809.
6. Kim, J. M., Parmar, K., Huang, M., Weinstock, D. M., Ruit, C. A., Kutok, J. L., and D'Andrea, A. D. (2009) Inactivation of murine Usp1 results in genomic instability and a Fanconi anemia phenotype, Dev Cell **16**, 314-320.
7. Chen, J., Dexheimer, T. S., Ai, Y., Liang, Q., Villamil, M. A., Inglese, J., Maloney, D. J., Jadhav, A., Simeonov, A., and Zhuang, Z. (2011) Selective and Cell-Active Inhibitors of the USP1/ UAF1 Deubiquitinase Complex Reverse Cisplatin Resistance in Non-small Cell Lung Cancer Cells, Chemistry & biology **18**, 1390-1400.

Patent Status:

US Provisional Patent Application No. 61/747,052 entitled "Inhibitors of the USP/UAF1 Deubiquitinase Complexes and Uses Thereof " filed December 28, 2012; Inventors: Thomas Dexheimer (NCATS), Ajit Jadhav (NCATS), Qin Liang (University of Delaware), David Maloney (NCATS), Andrew Rosenthal (NCATS), Anton Simeonov (NCATS), Zhihao Zhuang (University of Delaware) NIH Ref. No.: E-043-2013/0-US-01

PCT Application No. PCT/US2013/077804 entitled, "Inhibitors of the USP/UAF1 Deubiquitinase Complexes and Uses Thereof" filed December 26, 2013 Inventors: Thomas Dexheimer (NCATS), Ajit Jadhav (NCATS), Qin Liang (University of Delaware), Diane Luci (NCATS), David Maloney (NCATS), Andrew Rosenthal (NCATS), Anton Simeonov (NCATS), Zhihao Zhuang (University of Delaware) NIH Ref. No.: E-043-2013/0-PCT-02

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